

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61K 31/495, C07D 239/24	A1	(11) International Publication Number: WO 00/33844 (43) International Publication Date: 15 June 2000 (15.06.2000)
(21) International Application Number: PCT/US99/28537		Published
(22) International Filing Date: 03 December 1999 (03.12.1999)		
(30) Priority Data: 09/205,498 04 December 1998 (04.12.1998) US		
(60) Parent Application or Grant BERLEX LABORATORIES, INC. [J]; O. DAVEY, David, D. [J]; O. PHILLIPS, Gary, B. [J]; (O. DAVEY, David, D. [J]; O. PHILLIPS, Gary, B. [J]; O. ZELANO, Anthony, J.; O.		
(54) Title: ARYL AND HETEROCYCLYL SUBSTITUTED PYRIMIDINE DERIVATIVES AS ANTI-COAGULANTS (54) Titre: DERIVES DE PYRIMIDINE A SUBSTITUTION ARYLE ET HETEROCYCLE EN TANT QU'ANTICOAGULANTS		
(57) Abstract <p>This invention is directed to aryl and heterocycl substituted pyrimidine derivatives selected from formulae (I), (II) and (III), wherein Z₁, Z₂, R₁, R₂, R₃, R₄, R₅ and R₆ are defined herein. These compounds are useful as anti-coagulants.</p>		
(57) Abrégé <p>L'invention concerne des dérivés de pyrimidine à substitution aryle et hétérocyclyle choisis parmi les formules (I), (II) et (III), dans lesquelles Z₁, Z₂, R₁, R₂, R₃, R₄, R₅ et R₆ sont définis dans le descriptif. Ces composés sont utiles en tant qu'anticoagulants.</p>		

PCT

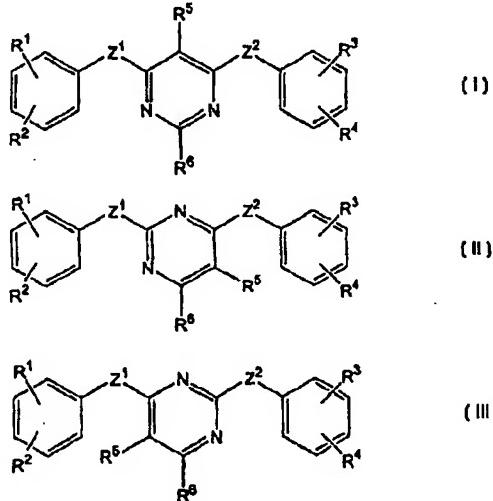
WORLD INTELLIGENT PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/495, C07D 239/24	A1	(11) International Publication Number: WO 00/33844 (43) International Publication Date: 15 June 2000 (15.06.00)
(21) International Application Number: PCT/US99/28537		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 3 December 1999 (03.12.99)		
(30) Priority Data: 09/205,498 4 December 1998 (04.12.98) US		
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/205,498 (CON) Filed on 4 December 1998 (04.12.98)		
(71) Applicant (for all designated States except US): BERLEX LABORATORIES, INC. [US/US]; 15049 San Pablo Avenue, P.O. Box 4099, Richmond, CA 94804-0099 (US).		Published With international search report.
(72) Inventors; and (75) Inventors/Applicants (for US only): DAVEY, David, D. [US/US]; 3813 Painted Pony Road, El Sobrante, CA 94803 (US). PHILLIPS, Gary, B. [US/US]; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US).		
(74) Agents: ZELANO, Anthony, J. et al.; Millen, White, Zelano & Branigan, P.C., Suite 1400, Arlington Courthouse Plaza 1, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).		

(54) Title: ARYL AND HETEROCYCLYL SUBSTITUTED PYRIMIDINE DERIVATIVES AS ANTI-COAGULANTS



(57) Abstract

This invention is directed to aryl and heterocyclyl substituted pyrimidine derivatives selected from formulae (I), (II) and (III), wherein Z¹, Z², R¹, R², R³, R⁴, R⁵ and R⁶ are defined herein. These compounds are useful as anti-coagulants.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

Des ription

5

10

15

20

25

30

35

40

45

50

55

**ARYL AND HETEROCYCLYL SUBSTITUTED PYRIMIDINE DERIVATIVES
AS ANTI-COAGULANTS**

10

5 **Field of the Invention**

The present invention is directed to aryl and heterocyclyl substituted pyrimidine derivatives and their pharmaceutically acceptable salts, which inhibit the enzyme, factor Xa, thereby being useful as anti-coagulants. It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use.

20

BACKGROUND OF THE INVENTION

Factor Xa is a member of the trypsin-like serine protease class of enzymes. A one-to-one binding of factors Xa and Va with calcium ions and phospholipid forms the prothrombinase complex which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin which polymerizes to form insoluble fibrin.

25

In the coagulation cascade, the prothrombinase complex is the convergent point of the intrinsic (surface activated) and extrinsic (vessel injury-tissue factor) pathways (*Biochemistry* (1991), Vol. 30, p. 10363; and *Cell* (1988), Vol. 53, pp. 505-518). The model of the coagulation cascade has been refined further with the discovery of the mode of action of tissue factor pathway inhibitor (TFPI) (*Seminars in Hematology* (1992), Vol. 29, pp. 159-161). TFPI is a circulating multi-domain serine protease inhibitor with three Kunitz-type domains which competes with factor Va for free factor Xa. Once formed, the binary complex of factor Xa and TFPI becomes a potent inhibitor of the factor VIIa and tissue factor complex.

30

Factor Xa can be activated by two distinct complexes, by tissue factor-VIIa complex on the "Xa burst" pathway and by the factor IXa-VIIa complex (TENase) of the "sustained Xa" pathway in the coagulation cascade. After vessel injury, the "Xa burst" pathway is activated via tissue factor (TF). Up regulation of the coagulation cascade occurs via increased factor Xa production via the "sustained Xa" pathway. Down regulation of the coagulation cascade occurs with the formation of the factor Xa-TFPI complex, which not only removes factor Xa but also inhibits further factor formation via the "Xa burst" pathway. Therefore, the coagulation cascade is naturally regulated by factor Xa.

40

50

55

5

- 2 -

10

The primary advantage of inhibiting factor Xa over thrombin in order to prevent coagulation is the focal role of factor Xa versus the multiple functions of thrombin. Thrombin not only catalyzes the conversion of fibrinogen to fibrin, factor VIII to VIIIa, factor V to Va, and factor XI to XIa, but also activates platelets, is a monocyte chemotactic factor, and mitogen for lymphocytes and smooth muscle cells. Thrombin activates protein C, the *in vivo* anti-coagulant inactivator of factors Va and VIIIa, when bound to thrombomodulin. In circulation, thrombin is rapidly inactivated by antithrombin III (ATIII) and heparin cofactor II (HCII) in a reaction which is catalyzed by heparin or other proteoglycan-associated glycosaminoglycans, whereas thrombin in tissues is inactivated by the protease, nexin. Thrombin carries out its multiple cellular activation functions through a unique "tethered ligand" thrombin receptor (*Cell* (1991), Vol. 64, p. 1057), which requires the same anionic binding site and active site used in fibrinogen binding and cleavage and by thrombomodulin binding and protein C activation. Thus, a diverse group of *in vivo* molecular targets compete to bind thrombin and the subsequent proteolytic events will have very different physiological consequences depending upon which cell type and which receptor, modulator, substrate or inhibitor binds thrombin.

15

20

25

30

35

40

45

Published data with the proteins antistasin and tick anti-coagulant peptide (TAP) demonstrate that factor Xa inhibitors are efficacious anti-coagulants (*Thrombosis and Haemostasis* (1992), Vol. 67, pp. 371-376; and *Science* (1990), Vol. 248, pp. 593-596).

The active site of factor Xa can be blocked by either a mechanism-based or a tight binding inhibitor (a tight binding inhibitor differs from a mechanism-based inhibitor by the lack of a covalent link between the enzyme and the inhibitor). Two types of mechanism-based inhibitors are known, reversible and irreversible, which are distinguished by ease of hydrolysis of the enzyme-inhibitor link (*Thrombosis Res.* (1992), Vol. 67, pp. 221-231; and *Trends Pharmacol. Sci.* (1987), Vol. 8, pp. 303-307). A series of guanidino compounds are examples of tight-binding inhibitors (*Thrombosis Res.* (1980), Vol. 19, pp. 339-349). Arylsulfonyl-arginine-piperidine-carboxylic acid derivatives have also been shown to be tight-binding inhibitors of thrombin (*Biochem.* (1984), Vol. 23, pp. 85-90), as well as a series of arylamidine-containing compounds, including 3-amidinophenylaryl derivatives (*Thrombosis Res.* (1983), Vol. 29, pp. 635-642) and bis(amidino)benzyl cycloketones (*Thrombosis Res.* (1980), Vol. 17, pp. 545-548). However, these compounds demonstrate poor selectivity for factor Xa.

50

55

5

Related Disclosures

European Published Patent Application 0 540 051 (Nagahara *et al.*) describes aromatic amidine derivatives. These derivatives are stated to be capable of showing a strong anticoagulant effect through reversible inhibition of factor Xa.

10

5 The synthesis of α,α' -bis(amidinobenzylidene)cycloalkanones and α,α' -bis(amidinobenzyl)cycloalkanones is described in *Pharmazie* (1977), Vol. 32, No. 3, pp. 141-145. These compounds are disclosed as being serine protease inhibitors.

15

U.S. Patent No. 5,451,700 (Morrissey *et al.*) describes amidino compounds. These compounds are stated to be useful as selective LTB₄ receptor antagonists.

20

10 U.S. Patent No. 5,612,363 (Mohan *et al.*) describes *N,N*-di(aryl) cyclic urea derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

15 U.S. Patent No. 5,633,381 (Dallas *et al.*) describes (Z,Z), (Z,E) and (E,Z) isomers of substituted *bis*(phenylmethylene)cycloketones. These compounds are disclosed as being factor Xa inhibitors, thereby being useful as anticoagulants.

25

20 PCT Published Patent Application WO/96/28427 (Buckman *et al.*) describes benzamidine derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

30

25 PCT Published Patent Application WO/97/21437 (Arnaiz *et al.*) describes naphthyl-substituted benzimidazole derivatives. These compounds are disclosed as being factor Xa inhibitors, thereby being useful as anticoagulants.

35

30 PCT Published Patent Application WO/97/29067 (Kochanny *et al.*) describes benzamidine derivatives that are substituted by amino acid and hydroxy acid derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

40

The above references, published patent applications and U.S. patents are herein incorporated in full by reference.

SUMMARY OF THE INVENTION

45

30 This invention is directed to compounds or their pharmaceutically acceptable salts which inhibit human factor Xa and are therefore useful as pharmacological agents for the treatment of disease-states characterized by thrombotic activity.

Accordingly, in one aspect, this invention provides compounds selected from the group consisting of the following formulae:

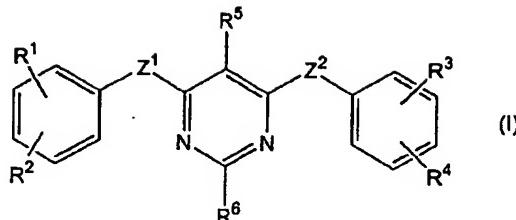
50

55

5

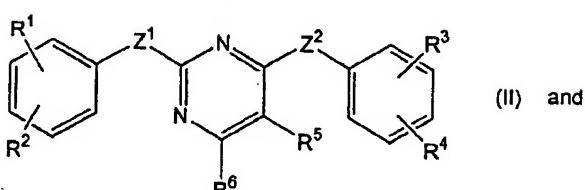
- 4 -

10

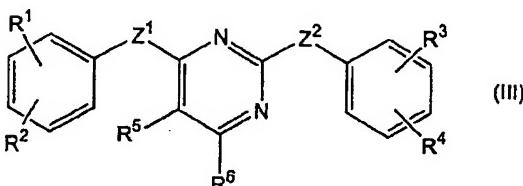


15

20



25



30

wherein:

Z¹ is -O-, -N(R⁷)-, -CH₂O- or -S(O)_n- (where n is 0 to 2);Z² is -O-, -N(R⁷)-, -OCH₂- or -S(O)_n- (where n is 0 to 2);5 R¹ and R⁴ are each independently hydrogen, halo, alkyl, nitro, -OR⁷, -C(O)OR⁷, -C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -N(R⁷)C(O)R⁷, or -N(H)S(O)₂R⁸;

35

R² is -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(NH)N(H)C(O)OR⁹, -C(NH)N(H)C(O)R⁷, -C(NH)N(H)S(O)₂R⁹, or -C(NH)N(H)C(O)N(H)R⁷;

40

R³ is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, -OR⁷, -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -CH(OH)C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -R¹⁰-N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -N(R⁷)C(O)R⁷, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

45

15 each R⁵ are independently hydrogen, halo, alkyl, haloalkyl, nitro, aralkoxy, -OR⁹, -R¹⁰-OR⁹, -N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -C(O)N(R⁷)CH₂C(O)N(R⁷)R⁸, -N(R⁷)C(O)N(R⁷)R⁸, -N(R⁷)C(O)R⁸, -N(R⁷)S(O)₂R⁹, or -N(R⁷)C(O)N(R⁷)-CH₂C(O)N(R⁷)R⁸;

50

5 -

- 5 each R⁶ is aryl (optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 10 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 15 each R⁹ is alkyl, aryl (optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 20 each R¹⁰ is independently an alkylene or alkylidene chain; as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.
- 25 In another aspect, this invention provides compositions useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the invention as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
- 30
- 35
- 40
- 45
- 50

5

- 6 -

10

In another aspect, this invention provides a method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

15

5 In another aspect, this invention provides a method of treating a human having a disease-state alleviated by the inhibition of factor Xa, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

10

In another aspect, this invention provides a method of inhibiting human factor Xa
10 *in vitro* by the administration of a compound of the invention.

20

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary,
15 the following terms have the meaning indicated:

25

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, *n*-propyl, 1-methylethyl (*i*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

30

"Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined above, e.g., methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*i*-propoxy), *n*-butoxy, *n*-pentoxy, 1,1-dimethylethoxy (*t*-butoxy), and the like.

35

"Alkoxycarbonyl" refers to a radical of the formula -C(O)OR_a where R_a is an alkyl radical as defined above, e.g., methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, 1-methylethoxycarbonyl (*i*-propoxycarbonyl), *n*-butoxycarbonyl, *n*-pentoxy carbonyl, 1,1-dimethylethoxycarbonyl (*t*-butoxycarbonyl), and the like.

40

"Alkanol" refers to a compound of the formula R_a-OH where R_a is an alkyl radical as defined above, e.g., methanol, ethanol, *n*-propanol, etc.

45

"Alkylene chain" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to six carbon atoms, e.g., methylene, ethylene, propylene, *n*-butylene and the like.

50

"Alkylidene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to six carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double

5

bond can exist between the first carbon of the chain and the rest of the molecule, e.g., ethylidene, propylidene, *n*-butylidene, and the like.

10

"Aryl" refers to a phenyl or naphthyl radical.

15

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above, substituted by R_b , an aryl radical, as defined above, e.g., benzyl.

20

"Aralkoxy" refers to a radical of the formula $-OR_c$ where R_c is an aralkyl radical as defined above, e.g., benzyloxy, and the like.

25

"Amidino" refers to the radical $-C(NH)NH_2$.

30

"Aminocarbonyl" refers to the radical $-C(O)NH_2$.

35

"Dialkylamino" refers to a radical of the formula $-N(R_a)R_b$ where each R_a is independently an alkyl radical as defined above, e.g., dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

40

"Dialkylaminocarbonyl" refers to a radical of the formula $-C(O)N(R_a)R_b$ where each R_a is independently an alkyl radical as defined above, e.g., dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

45

"Halo" refers to bromo, chloro, iodo or fluoro.

50

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

55

"Heterocycl" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocycl radical is not attached to pyrimidinyl moiety of the compounds of formula (I), (II) and (III) through a hetero atom. In addition, for purposes of this invention, the heterocycl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocycl radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom in the heterocycl radical may be optionally quaternized; and the heterocycl radical may be partially or fully saturated or aromatic. Examples of such heterocycl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl,

5

- 8 -

tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl; pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, Isothiazolyl, quinuclidinyl, Isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thieryl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl and oxadiazolyl.

20

"Heterocyclylalkyl" refers to a radical of the formula -R_a-R_d where R_a is an alkyl radical as defined above and R_d is a heterocyclyl radical as defined above, for example, (4-methylpiperazin-1-yl)methyl, (morpholin-4-yl)methyl, 2-(oxazolin-2-yl)ethyl, and the like.

25

"(1,2)-Imidazolyl" refers to an imidazolyl radical attached at either the 1- or 2-position.

30

"(1,2)-Imidazolinyl" refers to a 4,5-dihydroimidazolyl radical attached at either the 1- or the 2-position.

20

"Monoalkylamino" refers to a radical of the formula -NHR_a where R_a is an alkyl radical as defined above, e.g., methylamino, ethylamino, propylamino, and the like.

35

"Monoalkylaminocarbonyl" refers to a radical of the formula -C(O)NHR_a where R_a is an alkyl radical as defined above, e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

25

"(1,2)-Tetrahydropyrimidinyl" refers to a tetrahydropyrimidinyl radical attached at either the 1- or 2-position.

40

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example,

30

"optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

45

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

50

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or

5

otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like.

10

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an

15

10 organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary

20

15 amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydramine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, 30 theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

25

35 "Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for disease-states characterized by thrombotic activity. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

40

40 "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by thrombotic activity, and includes:

45

(i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it;

50

35 (ii) inhibiting the disease-state, *i.e.*, arresting its development; or

5

- 10 -

(iii) relieving the disease-state, i.e., causing regression of the disease-state.

10

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

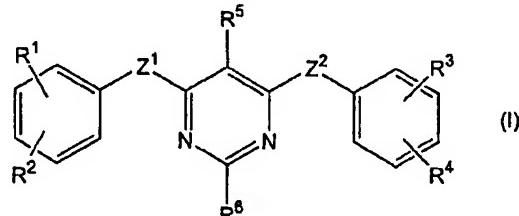
15

The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

20

The nomenclature used herein is a modified form of the I.U.P.A.C. system wherein the compounds of the invention are named as pyrimidinyl derivatives of benzamidine. For example, a compound of the invention selected from formula (I):

25



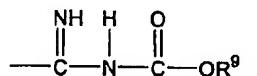
30

where Z¹ and Z² are both -O-, R¹ is hydroxy, R² is amidino, R³ is dimethylaminocarbonyl, R⁴ is hydrogen, R⁵ is hydrogen, and R⁶ is 4-methylphenyl is named herein as 4-hydroxy-3-[[6-(3-(dimethylaminocarbonyl)phenoxy)-2-(4-methylphenyl)pyrimidin-4-yloxy]benzamidine.

35

For purposes of this invention, parenthesis are used to denote substituents of a main atom of the substituent. For example, -C(NH)N(H)C(O)OR⁹ refers to the substituent of the formula:

40



45

Utility and Administration

A. Utility

50

The compounds of the invention are inhibitors of the serine protease, factor Xa, and are therefore useful in disease-states characterized by thrombotic activity based on factor Xa's role in the coagulation cascade (see Background of the Invention above). A

- 11 -

5

primary indication for the compounds is prophylaxis for long term risk following myocardial infarction. Additional Indications are prophylaxis of deep vein thrombosis (DVT) following orthopedic surgery or prophylaxis of selected patients following a transient ischemic attack. The compounds of the invention may also be useful for indications in which 10 coumadin is currently used, such as for DVT or other types of surgical intervention such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty. The compounds are also useful for the treatment of thrombotic complications associated with acute promyelocytic leukemia, diabetes, multiple myelomas, disseminated intravascular coagulation associated with septic shock, purpura fulminans associated infection, adult 15 respiratory distress syndrome, unstable angina, and thrombotic complications associated with aortic valve or vascular prosthesis. The compounds are also useful for prophylaxis 20 for thrombotic diseases, in particular in patients who have a high risk of developing such disease.

10

15

20

25

In addition, the compounds of the invention are useful as *in vitro* and *in vivo* diagnostic reagents for selectively inhibiting factor Xa without inhibiting other components of the coagulation cascade.

B. Testing

30

The primary bioassays used to demonstrate the inhibitory effect of the compounds 20 of the invention on factor Xa are simple chromogenic assays involving only serine protease, the compound of the invention to be tested, substrate and buffer (see, e.g., *Thrombosis Res.* (1979), Vol. 16, pp. 245-254). For example, four tissue human serine 35 proteases can be used in the primary bioassay, free factor Xa, prothrombinase, thrombin (IIa) and tissue plasminogen activator (tPA). The assay for tPA has been successfully 25 used before to demonstrate undesired side effects in the inhibition of the fibrinolytic process (see, e.g., *J. Med. Chem.* (1993), Vol. 36, pp. 314-319).

40

45

50

Another bioassay useful in demonstrating the utility of the compounds of the Invention in inhibiting factor Xa demonstrates the potency of the compounds against free factor Xa in citrated plasma. For example, the anticoagulant efficacy of the compounds of the invention will be tested using either the prothrombin time (PT), or activated partial thromboplastin time (aPTT) while selectivity of the compounds is checked with the thrombin clotting time (TCT) assay. Correlation of the K_i in the primary enzyme assay with the K_i for free factor Xa in citrated plasma will screen against compounds which interact with or are inactivated by other plasma components. Correlation of the K_i with the extension of the PT is a necessary *in vitro* demonstration that potency in the free factor Xa

5

- 12 -

Inhibition assay translates into potency in a clinical coagulation assay. In addition, extension of the PT in citrated plasma can be used to measure duration of action in subsequent pharmacodynamic studies.

10

For further information on assays to demonstrate the activity of the compounds of the invention, see R. Lottenberg *et al.*, *Methods in Enzymology* (1981), Vol. 80, pp. 341-361, and H. Ohno *et al.*, *Thrombosis Research* (1980), Vol. 19, pp. 579-588.

15

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

20

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

25

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

30

35

40

45

50

5

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, 10 5 polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

10

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active 15 15 ingredient disposed in a carrier that slowly dissolves within the body, e.g., polyoxyethylene glycols and polyethylene glycols (PEG), e.g., PEG 1000 (96%) and PEG 4000 (4%).

15

10 Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., a compound(s) of the invention (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a 20 20 carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

20

15 If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering 25 25 agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

30

Actual methods of preparing such dosage forms are known, or will be apparent, to 20 30 those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound 35 35 of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of factor Xa in accordance with the teachings of this invention.

35

25 The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic 40 40 stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease-states; and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.14 mg to about 45 45 14.3 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight 50 50 per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body weight per

5

- 14 -

10

day. For example, for administration to a 70 kg person, the dosage range would be from about 10 mg to about 1.0 gram per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 50 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

5

Preferred Embodiments

15

Of the compounds of the invention as set forth above in the Summary of the Invention, a preferred group of compounds are those compounds wherein Z¹ is -O-, -CH₂O- or -S(O)_n- (where n is 0 to 2); Z² is -O-, -OCH₂- or -S(O)_n- (where n is 0 to 2); R¹ and R⁴ are each independently hydrogen, halo, alkyl or -OR⁷; R² is -C(NH)NH₂, -C(NH)N(H)S(O)₂R⁸, or -C(NH)N(H)C(O)N(H)R⁷; R³ is ureido, guanidino, -N(R')R⁶, -N(R')C(O)R⁷, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); each R⁵ are independently hydrogen, halo, alkyl or haloalkyl; each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); each R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and each R¹⁰ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is

20

25

30

35

40

45

50

- 15 -

5

optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

10

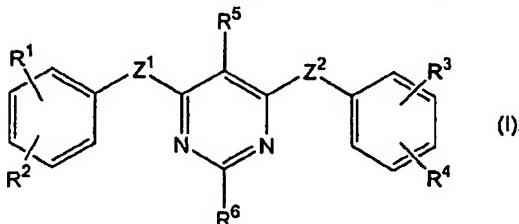
Of this group of compounds, a preferred subgroup of compounds are those 5 compounds wherein Z¹ is -O-; Z² is -O-; R¹ is hydrogen or -OR⁷; R² is -C(NH)NH₂; R³ is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R⁴ is hydrogen; each R⁵ is hydrogen or halo; and each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, 10 carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, 15 carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or 20 dialkylaminocarbonyl); and each R⁷ is independently hydrogen or alkyl.

20

Of this subgroup of compounds, a preferred class of compounds are those 35 compounds wherein Z¹ is -O-; Z² is -O-; R¹ is -OR⁷; R² is -C(NH)NH₂; R³ is (1,2)-imidazolyl (optionally substituted by methyl) or (1,2)-imidazolinyl (optionally substituted by methyl); R⁴ is hydrogen; R⁵ is hydrogen; and R⁶ is aryl (optionally 40 substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and R⁷ is hydrogen or alkyl.

40

Of this class of compounds, a preferred subclass of compounds are those 45 compounds wherein the compound is selected from the formula (I):



50

30

5

- 16 -

10

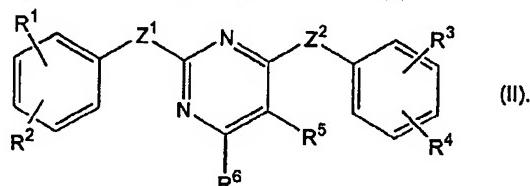
Of this subclass of compounds, preferred compounds are those compounds wherein R¹ is hydroxy; R³ is 1-methylimidazolin-2-yl; and R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

15

Of these preferred compounds, a more preferred compound is 4-hydroxy-3-[(6-(1-methylimidazolin-2-yl)phenoxy)-2-(phenyl)pyrimidin-4-yl]oxy]benzamidine.

20

Of the class of compounds described above, another preferred subclass of compounds are those compounds selected from formula (II):



25

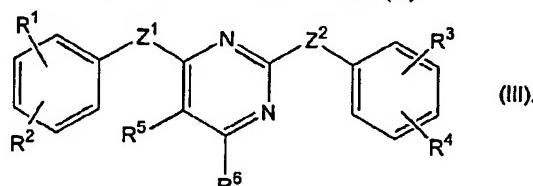
30

Of this subclass of compounds, preferred compounds are those compounds wherein R¹ is hydroxy; R³ is 1-methylimidazolin-2-yl; and R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

35

Of these preferred compounds, a more preferred compound is 4-hydroxy-3-[(4-(1-methylimidazolin-2-yl)phenoxy)-6-(phenyl)pyrimidin-2-yl]oxy]benzamidine.

Of the class of compounds described above, another preferred subclass of compounds are those compounds selected from formula (III):



40

45

Of this subclass of compounds, preferred compounds are those compounds wherein R¹ is hydroxy; R³ is 1-methylimidazolin-2-yl; and R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

50

55

5

- 17 -

Of these preferred compounds, a more preferred compound is 4-hydroxy-3-[2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(phenyl)pyrimidin-4-yl]oxy]benzamidine.

10

Preparation of Compounds of The Invention

15

As a matter of convenience, the following description of the preparation of the compounds of the invention is directed to the preparation of compounds of the invention where Z^1 and Z^2 are both -O-, and R^2 is $-C(NH)NH_2$. It is understood, however, that similar synthetic processes may be used to prepare other compounds of formula (I), (II), and (III). It is also understood that in the following description, combinations of substituents and/or variables (e.g., R^7 and R^8) on the depicted formulae are permissible only if such combinations result in stable compounds.

20

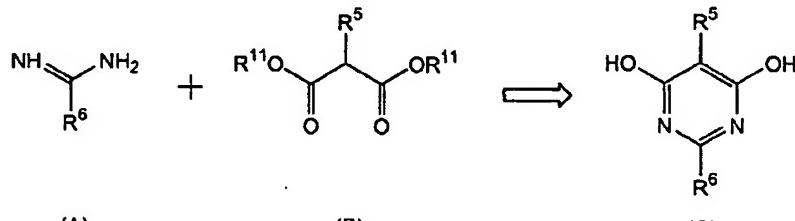
Preparation of Compounds of Formula (C):

25

Compounds of formula (C) are intermediates in the preparation of compounds of the invention and are prepared as described below in Reaction Scheme 1 where R^5 and R^6 are as described above in the Summary of the Invention and R^{11} is alkyl or aralkyl:

Reaction Scheme 1

30



35

(A)

(B)

(C)

40

Compounds of formula (A) and formula (B) are commercially available, or may be prepared according to methods known to those skilled in the art.

45

In general, compounds of formula (C) are prepared by first treating an alkanol, preferably ethanol, to a molar excess amount of an alkaline metal, preferably sodium. After the metal is completely dissolved, a compound of formula (A) and a compound of formula (B) are added in equimolar amounts to the solution at ambient temperature. The resulting reaction mixture is heated to reflux for about 4 to about 6 hours, preferably for about 4 hours. The solvent is removed and a strong acid, preferably hydrochloric acid, is added to the reaction mixture to afford a precipitate, which is collected and dried to afford the compound of formula (C).

50

55

5

- 18 -

10

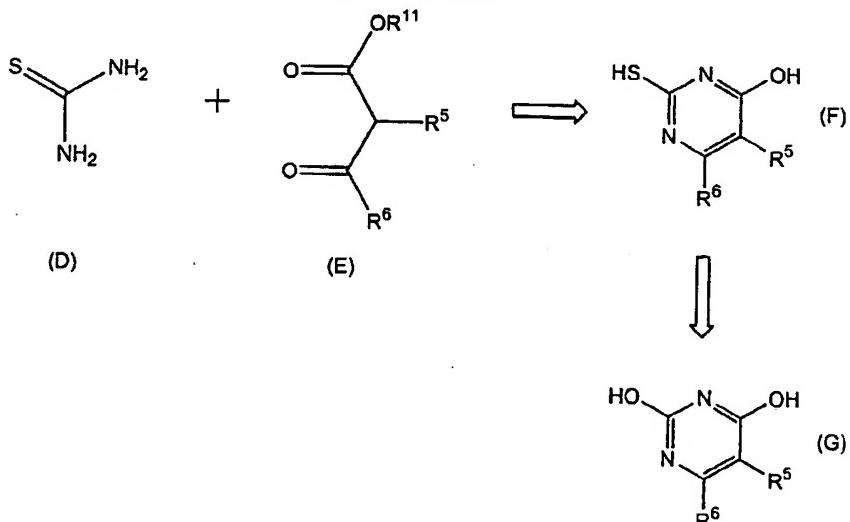
Preparation of Compounds of Formula (G):

Compounds of formula (G) are intermediates in the preparation of compounds of the invention and are prepared as illustrated below in Reaction Scheme 2 wherein R⁵ and R⁶ are as described above in the Summary of the Invention and R¹¹ is alkyl or aralkyl:

5

Reaction Scheme 2

15



88

25

30

Compounds of formula (D) and formula (E) are commercially available, or may be prepared according to methods known to those of ordinary skill in the art.

36

10 In general, compounds of formula (G) are prepared by first treating an alkanol, preferably ethanol, to a molar excess amount of an alkaline metal, preferably sodium. After the metal is completely dissolved, a compound of formula (D) and a compound of formula (E) in equimolar amounts are added to the solution. The reaction mixture is heated for about 8 to about 16 hours, preferably for about 16 hours. The solvent is
15 removed and the residue dissolved in water. A strong acid, preferably hydrochloric acid, is added to the solution and the resulting precipitate is collected and dried to form a compound of formula (G).

45

Preparation of Compounds of Formula (H):

50

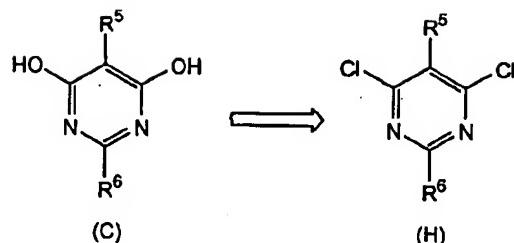
20 Compounds of formula (H) are intermediates in the preparation of the compounds of the invention and are prepared as illustrated below in Reaction Scheme 3 wherein R⁵ and R⁶ are as described above in the Summary of the Invention:

55

5

- 19 -

Reaction Scheme 3



Compounds of formula (C) are prepared by methods described herein.

In general, compounds of formula (H) are prepared by treating a compound of formula (C) with a slight molar excess of a chlorinating agent, preferably phosphorus oxychloride, in the presence of a base, such as *N,N*-diethylaniline. The resulting reaction mixture is refluxed for about 2 to about 4 hours, preferably for about 3 hours, and then ice is added to the solution to afford a precipitate, which is collected and dried to afford a

10 In a similar manner, compounds of formula (G) may be chlorinated to form the dichloro-substituted compounds.

30

Preparation of Compounds of Formula (Ia):

Compounds of formula (la) are compounds of the invention selected from formula (I), and are prepared as illustrated below in Reaction Scheme 4 where R¹, R³, R⁴, R⁵ and R⁶ are as described above in the Summary of the Invention. Prior to Step 1 compounds of formula (H), formula (J) and formula (L) wherein the R¹, R³, R⁴, R⁵ and R⁶ substituents contain additional reactive hydroxy or amino groups may be treated with the appropriate oxygen- or nitrogen-protecting group according to methods known to those skilled in the art, such as those described in Greene, T.W., *Protective Groups in Organic Synthesis* (1981), John Wiley & Sons, New York, New York. Such protected substituents will be deprotected during the reaction conditions of Step 3 to form the desired R¹, R³, R⁴, R⁵ and R⁶ substituents. Alternatively, compounds of formula (H), formula (J) and formula (L) may already be present in an oxygen- or nitrogen-protected form and may be deprotected by methods known to those skilled in the art or, as a result of the reaction conditions of Step 3, may become deprotected to form the desired substituent.

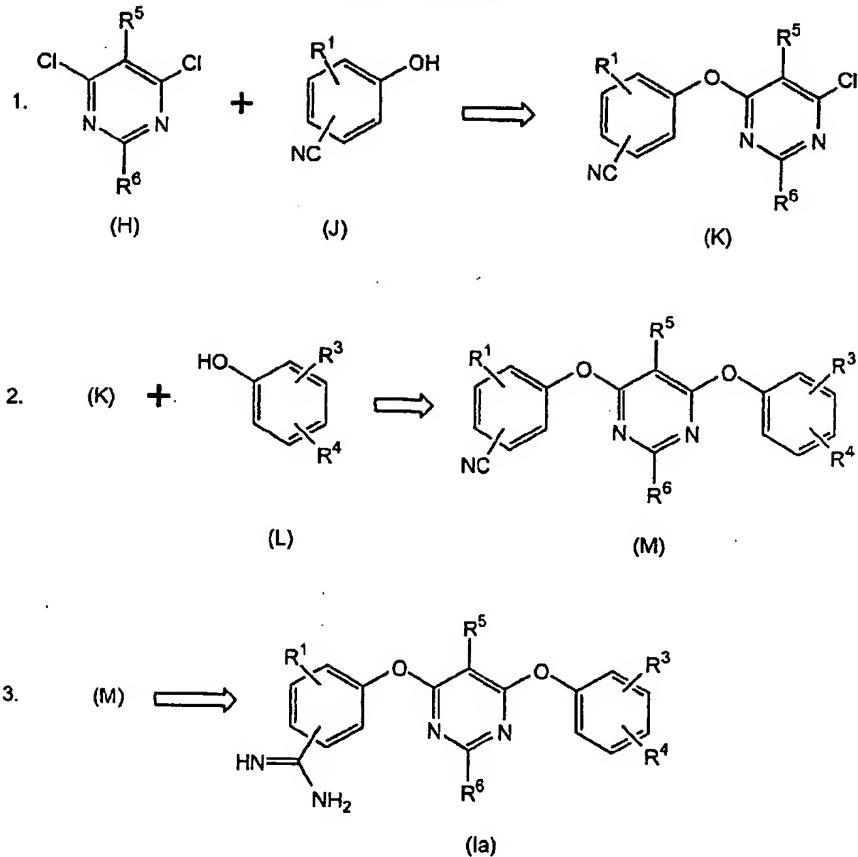
50

55

5

- 20 -

Reaction Scheme 4



Compounds of formula (H) are prepared by methods disclosed herein. Compounds of formula (J) and formula (L) are commercially available or may be prepared according to methods known to those skilled in the art.

In general, the compounds of formula (Ia) are prepared by first treating a compound of formula (H) in an aprotic solvent, for example, acetonitrile, with an equimolar amount of a compound of formula (J) in the presence of a base, for example, cesium carbonate, at temperatures between about 20°C and 120°C, preferably at ambient temperature, for a period of time sufficient to complete the desired reaction as monitored by thin layer chromatography (TLC). The compound of formula (K) is then isolated from

55

the reaction mixture by standard isolation techniques, such as extraction, *in vacuo* removal of solvent, and flash chromatography.

The compound of formula (K) in an aprotic solvent, for example, DMSO, is then treated with an equimolar amount of a compound of formula (L) in the presence of a base, for example, cesium carbonate, at temperatures between about 20°C and 120°C, preferably at about 50°C, for a period of time sufficient to complete the desired reaction, for example, for about 24 hours. The reaction mixture is cooled to ambient temperature and the compound of formula (M) is then isolated from the reaction mixture through standard isolation techniques, such as extraction, *in vacuo* removal of solvent, and flash chromatography.

The compound of formula (M) is dissolved in an anhydrous alkanol, preferably ethanol, and then anhydrous mineral acid, preferably HCl, is added to the solution over a period of time sufficient to saturate the acid into the solution while maintaining the reaction temperatures at about -78°C. After saturation is complete, the reaction vessel is sealed and the reaction mixture is allowed to warm to ambient temperature and stirred between 12 and 24 hours, preferably for about 18 hours. The solvent is removed *in vacuo* and the resulting residue is dissolved in fresh anhydrous alkanol, preferably ethanol, and then treated with anhydrous ammonia (gas) at temperatures from between ambient temperature and about 100°C from about 1 to about 48 hours, preferably at about 60°C and for about 2 hours. The compound of formula (Ia) is then isolated from the reaction mixture by standard isolation techniques, for example, *in vacuo* removal of solvent and purification by high performance liquid chromatography (HPLC). During this last step, compounds of formula (G) where any R¹, R³, R⁴, R⁵, or R⁶ substituent is in an oxygen- or nitrogen-protected form are deprotected to form compounds of formula (Ia) where R¹, R³, R⁴, R⁵ or R⁶ is as defined above in the Summary of the Invention.

Alternatively, instead of treating the resulting residue above with anhydrous ammonia (gas), the resulting residue may be treated with a compound of the formula NH₂OR⁷ to afford the corresponding compound of formula (Ia) wherein R² is -C(NH)N(H)OR⁷.

Compounds of formula (Ia) wherein R³ is -C(NH)NH₂ or -C(NH)N(H)OR⁷ are produced from the corresponding cyano compounds in a similar manner as that described above for compound of formula (M).

Compounds of formula (Ia) wherein R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains an alkoxy carbonyl group or a -C(O)OR⁷ group where R⁷ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino,

5

monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) may be prepared from the corresponding activated acid, such as an acid halide by techniques known to those of ordinary skill in the art.

10

Compounds of formula (Ia) wherein R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains an aminocarbonyl group, a monoalkylaminocarbonyl group, a dialkylaminocarbonyl group, a -C(O)N(R⁷)R⁸ group or a -C(O)OR⁷ group (where each R⁷ or R⁸ is independently alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) may also be hydrolyzed under acidic conditions to prepare corresponding compounds of the invention where R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains a carboxy or a -C(O)OH group.

15

Compounds of formula (Ia) wherein R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains a carboxy group, an alkoxy carbonyl group, or a -C(O)OR⁷ group where R⁷ is hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) may also be amidated under standard amidation conditions to form the corresponding compounds of formula (Ia) where R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains an aminocarbonyl group, a monoalkylaminocarbonyl group, a dialkylaminocarbonyl group or a -C(O)N(R⁷)R⁸ group where R⁷ and R⁸ are independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

20

Compounds of formula (Ia) wherein R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains an aminocarbonyl group, a monoalkylaminocarbonyl group, a dialkylaminocarbonyl group or a -C(O)N(R⁷)R⁸ group where R⁷ and R⁸ are independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) may also be reduced under standard conditions to produce the corresponding compounds of formula (Ia) where R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸ or R⁹ contains an amino group, which may also be treated with the appropriate alkylating agents or acylating

25

30

35

40

45

50

5

agents to afford the corresponding compounds of formula (Ia) where R¹, R³, R⁴, R⁶, R⁸, R⁷, R⁹ or R⁹ contains a monoalkylamino group, a dialkylamino group, a -N(R⁷)R⁸ group or a -N(R⁷)C(O)R⁷ where each R⁷ and R⁸ is independently hydrogen, alkyl, or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

10

Compounds of formula (Ia) may also be further treated with the appropriate acid

15

halide, preferably acid chloride, or with the appropriate acid anhydride or an equivalent, to yield compounds of the invention wherein R² is -C(NH)N(H)C(O)R⁷ where R⁷ is hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

20

Alternatively, compounds of formula (Ia) may further be treated with a compound of formula Cl-C(O)-OR⁹ or its functional equivalent to yield compounds of the invention where R² is -C(NH)N(H)C(O)OR⁹ where R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

25

Alternatively, compounds of formula (Ia) may further be treated with a compound of formula Cl-C(O)-OR⁹ or its functional equivalent to yield compounds of the invention where R² is -C(NH)N(H)C(O)OR⁹ where R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

30

Alternatively, compounds of formula (Ia) may further be treated with a compound of formula Cl-C(O)-OR⁹ or its functional equivalent to yield compounds of the invention where R² is -C(NH)N(H)C(O)OR⁹ where R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

35

Alternatively, compounds of formula (Ia) may also be further treated with compounds of the formula R⁹-S(O)₂-imidazole (where R⁹ is defined above in the Summary of the Invention) in a polar solvent, such as methylene chloride, at ambient temperature to afford compounds of the invention where R² is -C(NH)N(H)S(O)₂R⁹ where R⁹ is defined above in the Summary of the Invention.

40

Alternatively, compounds of formula (Ia) may be further treated with an appropriately N-R⁷-substituted phenylcarbamate in a polar solvent, preferably methylene chloride, at ambient temperature, for about 6 to 24 hours, preferably for about 12 hours, to afford compounds of the invention where R² is -C(NH)N(H)C(O)N(H)R⁷ where R⁷ is defined above in the Summary of the Invention.

45

50

5

- 24 -

Compounds of formula (Ia) which contain an unoxidized sulfur atom may be oxidized with the appropriate oxidizing agent to produce compounds containing oxidized sulfur (*i.e.*, $-S(O)_n$ - where n is 1 or 2).

10

In a similar manner to the reactions described above, compounds of formula (II) and (III) may be prepared.

15

All compounds of the invention as prepared above which exist in free base or acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid. Salts of the compounds prepared above may be converted to their free base or acid form by standard techniques.

10

* * * *

20

The following specific preparations and examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

15

25

PREPARATION 1

Compounds of Formula (C)

A. To ethanol (200 mL) was added sodium (7.9 g, 34 mmol). After dissolution, benzamidine hydrochloride (20.0 g, 0.128 mmol) and diethyl malonate (20 mL, 132 mmol) were added. The reaction was heated for 4 hours and the solvent was removed *in vacuo*. Hydrochloric acid was added and a precipitate formed. The solid was collected and dried in a vacuum oven to give 10.8 g (45%) of 2-phenyl-4,6-dihydroxypyrimidine.

35

B. In a similar manner, the following compounds of formula (C) are made:

- 25 2-(4-methylphenyl)-4,6-dihydroxypyrimidine;
- 2-(3-chlorophenyl)-4,6-dihydroxypyrimidine;
- 40 2-(4-phenylphenyl)-4,6-dihydroxypyrimidine;
- 2-(4-(benzyloxy)phenyl)-4,6-dihydroxypyrimidine;
- 2-(4-methoxyphenyl)-4,6-dihydroxypyrimidine;
- 45 2-(4-(benzyloxycarbonylamino)phenyl)-4,6-dihydroxypyrimidine;
- 2-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-4,6-dihydroxypyrimidine;
- 2-(4-(dimethylamino)phenyl)-4,6-dihydroxypyrimidine;
- 2-(4-(aminocarbonyl)phenyl)-4,6-dihydroxypyrimidine;
- 50 2-(1-(benzyloxycarbonyl)piperidin-4-yl)-4,6-dihydroxypyrimidine;
- 35 2-(1-ethylpiperidin-4-yl)-4,6-dihydroxypyrimidine;

55

5

- 25 -

2-(pyridin-2-yl)-4,6-dihydroxypyrimidine;
2-(imidazolin-2-yl)-4,6-dihydroxypyrimidine; and
2-(piperidin-1-yl)methyl-4,6-dihydroxypyrimidine.

10

C. In a manner similar to that described above, other compounds of formula

5 (C) may be prepared.

PREPARATION 2

15

Compounds of Formula (G)

A. To ethanol (100 mL) was added sodium (3.3 g, 14 mmol). After 10 dissolution, thiourea (10.7 g, 14 mmol) and ethyl benzoylacetate (24 mL, 14 mmol) were added. The reaction was heated for 16 hours and the solvent was removed *in vacuo*. Water was added to dissolve the residue and hydrochloric acid was added and a precipitate formed. The solid was collected and dried in a vacuum oven to give 16 g (56%) of 2-mercaptop-4-hydroxy-6-phenylpyrimidine.

20

B. 2-Mercapto-4-hydroxy-6-phenylpyrimidine (8.6 g, 42 mmol) and chloroacetic acid (8.5 g, 90 mmol) were slurried in water (100 mL). After refluxing the mixture for 24 hours, hydrochloric acid was added and the precipitate was isolated by filtration. The solid was dried in a vacuum oven to give 6.6 g (83%) of 2,4-dihydroxy-6-phenylpyrimidine.

25

C. In a similar manner, the following compounds of formula (G) are made:

6-(4-methylphenyl)-2,4-dihydroxypyrimidine;

6-(3-chlorophenyl)-2,4-dihydroxypyrimidine;

6-(4-phenylphenyl)-2,4-dihydroxypyrimidine;

6-(4-(benzyloxy)phenyl)-2,4-dihydroxypyrimidine;

25 6-(4-methoxyphenyl)-2,4-dihydroxypyrimidine;

6-(4-(benzyloxycarbonylamino)phenyl)-2,4-dihydroxypyrimidine;

6-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-2,4-dihydroxypyrimidine;

6-(4-(dimethylamino)phenyl)-2,4-dihydroxypyrimidine;

6-(4-(aminocarbonyl)phenyl)-2,4-dihydroxypyrimidine;

30 6-(1-(benzyloxycarbonyl)piperidin-4-yl)-2,4-dihydroxypyrimidine;

6-(1-ethylpiperidin-4-yl)-2,4-dihydroxypyrimidine;

6-(pyridin-2-yl)-2,4-dihydroxypyrimidine;

6-(imidazolin-2-yl)-2,4-dihydroxypyrimidine; and

6-(piperidin-1-yl)methyl-2,4-dihydroxypyrimidine.

45

50

55

5

- 26 -

D. In a manner similar to that described above in Paragraphs A and B, other compounds of formula (G) may be prepared.

10

PREPARATION 3

5

Compounds of Formula (H)

A. To 4,6-dihydroxy-2-phenylpyrimidine (10.8 g, 57 mmol) was added phosphorous oxychloride (58 mL, 62 mmol) and *N,N*-diethylaniline (16 mL, 10 mmol). After refluxing for 3 hours, ice was added to the solution and a precipitate formed. The solid was collected and dried in a vacuum oven to give 11.4 g (88%) of 4,6-dichloro-2-phenylpyrimidine; m.p. 94-95°C.

15

B. In a similar manner, the following compound was made:
2,4-dichloro-6-phenylpyrimidine; m.p. 85-87°C.

20

C. In a similar manner, the following compounds of formula (H) are made:
2-(4-methylphenyl)-4,6-dichloropyrimidine;

25

2-(3-chlorophenyl)-4,6-dichloropyrimidine;
2-(4-phenylphenyl)-4,6-dichloropyrimidine;
2-(4-(benzyloxy)phenyl)-4,6-dichloropyrimidine;
2-(4-methoxyphenyl)-4,6-dichloropyrimidine;
2-(4-(benzyloxycarbonylamino)phenyl)-4,6-dichloropyrimidine;

30

2-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-4,6-dichloropyrimidine;
2-(4-(dimethylamino)phenyl)-4,6-dichloropyrimidine;
2-(4-(aminocarbonyl)phenyl)-4,6-dichloropyrimidine;
2-(1-(benzyloxycarbonyl)piperidin-4-yl)-4,6-dichloropyrimidine;
2-(1-ethylpiperidin-4-yl)-4,6-dichloropyrimidine;

35

25 2-(pyridin-2-yl)-4,6-dichloropyrimidine;
2-(imidazolin-2-yl)-4,6-dichloropyrimidine; and
2-(piperidin-1-yl)methyl-4,6-dichloropyrimidine.

40

D. In a manner similar to that described above in Paragraphs A, the following intermediates of the compounds of the invention are prepared:

45

30 6-(4-methylphenyl)-2,4-dichloropyrimidine;
6-(3-chlorophenyl)-2,4-dichloropyrimidine;
6-(4-phenylphenyl)-2,4-dichloropyrimidine;
6-(4-(benzyloxy)phenyl)-2,4-dichloropyrimidine;
6-(4-methoxyphenyl)-2,4-dichloropyrimidine;

50

35 6-(4-(benzyloxycarbonylamino)phenyl)-2,4-dichloropyrimidine;

- 27 -

5

- 6-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-2,4-dichloropyrimidine;
6-(4-(dimethylamino)phenyl)-2,4-dichloropyrimidine;
6-(4-(aminocarbonyl)phenyl)-2,4-dichloropyrimidine;
6-(1-(benzyloxycarbonyl)piperidin-4-yl)-2,4-dichloropyrimidine;
5 6-(1-ethylpiperidin-4-yl)-2,4-dichloropyrimidine;
6-(pyridin-2-yl)-2,4-dichloropyrimidine;
6-(imidazolin-2-yl)-2,4-dichloropyrimidine; and
15 6-(piperidin-1-yl)methyl-2,4-dichloropyrimidine.

E. In a similar manner, other intermediates of the compounds of the
10 invention may be prepared.

20

PREPARATION 4

Compounds of Formula (K)

A. To 4,6-dichloro-2-phenylpyrimidine (1.5 g, 6.7 mmol) in acetonitrile (20
15 mL) was added Cs₂CO₃ (2.4 g, 7.4 mmol) and 3-hydroxy-4-(benzyloxy)benzonitrile (1.5
g, 6.5 mmol). After stirring for 24 hours, water was added to the reaction mixture and
the resulting solid was collected by suction filtration to give 2.6 g of 3-[(6-chloro-2-
phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

30

B. In a similar manner, the following intermediates of compounds of the
20 invention were made:
3-[(6-chloro-4-phenylpyrimidin-2-yl)oxy]-4-(benzyloxy)benzonitrile; and
3-[(2-chloro-6-phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

35

C. In a similar manner, the following compounds of formula (K) are made:
3-[(2-(4-methylphenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
25 3-[(2-(3-chlorophenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-phenylphenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
40 3-[(2-(4-(benzyloxy)phenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-methoxyphenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-(benzyloxycarbonylamino)phenyl)-6-chloropyrimidin-4-yl)oxy]-4-
30 (benzyloxy)benzonitrile;
3-[(2-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-6-chloropyrimidin-4-yl)oxy]-4-
45 (benzyloxy)benzonitrile;
3-[(2-(4-(dimethylamino)phenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-(aminocarbonyl)phenyl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

50

55

5 - 28 -

- 3-[(2-(1-(benzyloxycarbonyl)piperidin-4-yl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(1-ethylpiperidin-4-yl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
10 3-[(2-(2-pyridin-2-yl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
5 3-[(2-(imidazolin-2-yl)-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile; and
3-[(2-(piperidin-1-yl)methyl-6-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

D. In a similar manner to that described above, the following intermediates of the compounds of the invention are made:

- 15 3-[(6-(4-methylphenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
10 3-[(6-(3-chlorophenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
20 3-[(6-(4-phenylphenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(4-(benzyloxy)phenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(4-methoxyphenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(4-(benzyloxycarbonylamino)phenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
25 3-[(6-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(4-(dimethylamino)phenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
30 3-[(6-(4-(aminocarbonyl)phenyl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
20 3-[(6-(1-(benzyloxycarbonyl)piperidin-4-yl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(1-ethylpiperidin-4-yl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
35 3-[(6-(pyridin-2-yl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(6-(imidazolin-2-yl)-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile; and
25 3-[(6-(piperidin-1-yl)methyl-2-chloropyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

E. In a similar manner to that described above, other intermediates of the compounds of the invention may be prepared.

PREPARATION 5

Compounds of Formula (M)

- A. To 3-[(6-chloro-2-phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile (1.0 g, 2.4 mmol) in DMSO (12 mL) was added Cs₂CO₃ (0.8 g, 2.5 mmol) and 2-(3-hydroxyphenyl)-1-methylimidazole (0.44 g, 2.5 mmol). After stirring in an oil bath at 50°C for 24 hours, the reaction was partitioned with water and ethyl acetate. The layers 45 were separated, washed with water and brine, dried (Na₂SO₄), and the solvent was
50 35

- 29 -

5

removed *in vacuo*. The residue was chromatographed on silica gel with CH₂Cl₂/MeOH/NH₄OH (120/5/1) to give 0.5 g of 3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

10

B. In a similar manner, the following compounds of formula (M) were made:

- 5 3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-4-phenylpyrimidin-2-yl)oxy]-4-(benzyloxy)benzonitrile; and
3-[(2-[3-(1-methylimidazolin-2-yl)phenoxy]-6-phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.
- 15 C. In a similar manner, the following compounds of formula (M) are made:
10 3-[(2-(4-methylphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
20 3-[(2-(3-chlorophenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-phenylphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
25 3-[(2-(4-(benzyloxy)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(4-methoxyphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
30 20 3-[(2-(4-(benzyloxycarbonylamino)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(3-((methyl)(benzyloxycarbonyl)amino)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
35 3-[(2-(4-(dimethylamino)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
25 3-[(2-(4-(aminocarbonyl)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
40 3-[(2-(1-benzyloxycarbonyl)piperidin-4-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
30 3-[(2-(1-ethylpiperidin-4-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
45 3-[(2-(pyridin-2-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;
3-[(2-(imidazolin-2-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile; and
50 35

55

5

- 30 -

3-[(2-(piperidin-1-yl)methyl-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

10

D. In a manner similar to that described above, the following intermediates of the compounds of the invention are prepared:

15

5 3-[(6-(4-methylphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

20

3-[(6-(3-chlorophenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

25

3-[(6-(4-phenylphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

30

3-[(6-(4-(benzyloxy)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

35

3-[(6-(4-methoxyphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

40

15 3-[(6-(4-(benzyloxycarbonylamino)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

3-[(6-(3-(methyl)(benzyloxycarbonyl)amino)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

45

3-[(6-(4-(dimethylamino)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

3-[(6-(4-(aminocarbonyl)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

50

3-[(6-(1-(benzyloxycarbonyl)piperidin-4-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

55

25 3-[(6-(1-ethylpiperidin-4-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

3-[(6-(pyridin-2-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile;

60

3-[(6-(imidazolin-2-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile; and

3-[(6-(piperidin-1-yl)methyl-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile.

E. In a similar manner to that described above, other intermediates of the compounds of the invention may be prepared.

50

35

5

- 31 -

EXAMPLE 1**Compounds of Formula (I), (II), and (III)**

A. To 3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]-4-(benzyloxy)benzonitrile (0.4 g, 0.7 mmol) dissolved in ethanol (15 mL) and cooled in a dry ice/isopropanol bath was bubbled HCl (g). After the solution was saturated the reaction flask was sealed and allowed to warm to ambient temperature and stirred for 18 hours. The solvent was removed *in vacuo* and the residue was triturated with ether. The ether was decanted off and the residue was dissolved in ethanol (6 mL). The solution was cooled in a dry ice/isopropanol bath and ammonia (g) was bubbled into the solution. The reaction flask was sealed and heated in an oil bath at 60°C for 2 hours. The solvent was removed *in vacuo* and the residue was purified by HPLC on a C18 Dynamax column with a 10-40% acetonitrile in water gradient with 0.1% trifluoroacetic acid to give 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine, trifluoroacetic acid salt, as a pure trifluoroacetic acid salt; NMR (DMSO-d₆) 11.2 (s, 1), 10.4 (s, 1), 9.1 (s, 2), 8.9 (s, 2), 7.8 (m, 7), 7.4 (m, 4), 7.2 (d, 1), 6.7 (s, 1), 4.1 (m, 2), 4.0 (m, 2), 3.1 (s, 3) ppm.

B. In a similar manner, the following compounds of the invention were made:

4-hydroxy-3-[(4-[3-(1-methylimidazolin-2-yl)phenoxy]-6-phenylpyrimidin-2-yl)oxy]benzamidine and 4-hydroxy-3-[(2-[3-(1-methylimidazolin-2-yl)phenoxy]-6-phenylpyrimidin-4-yl)oxy]benzamidine, trifluoroacetic acid salt, NMR (DMSO-d₆) 10.4 (s, 1), 9.1 (m, 2), 8.8 (m, 2), 8.0 (d, 2), 7.4-7.8 (m, 11), 7.1 (m, 1), 4.0 (m, 4), 3.1 (s, 3) ppm.

C. In a similar manner, the following compounds of the invention are made:

3-[(2-(4-methylphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
3-[(2-(3-chlorophenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
3-[(2-(4-phenylphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
3-[(2-(4-hydroxyphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
3-[(2-(4-methoxyphenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;

50

55

5

- 32 -

- 3-[(2-(4-aminophenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 3-[(2-(3-(methylamino)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 5 3-[(2-(4-(dimethylamino)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 10 3-[(2-(4-(aminocarbonyl)phenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 15 3-[(2-(4-(aminophenyl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 20 3-[(2-(1-ethylpiperidin-4-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 25 3-[(2-(pyridin-2-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 30 3-[(2-(imidazolin-2-yl)-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 20 3-[(2-(piperidin-1-yl)methyl-6-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 35 3-[(6-(4-methylphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 25 3-[(6-(3-chlorophenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 40 3-[(6-(4-phenylphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 25 3-[(6-(4-hydroxyphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 45 3-[(6-(4-methoxyphenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 30 3-[(6-(4-aminophenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 45 3-[(6-(3-(methylamino)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;
- 50 3-[(6-(4-(dimethylamino)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-hydroxybenzamidine;

- 33 -

- 5 3-[(6-(4-(aminocarbonyl)phenyl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-
yloxy]-4-hydroxybenzamidine;
10 3-[(6-(piperidin-4-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-
hydroxybenzamidine;
5 3-[(6-(1-ethylpiperidin-4-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-
hydroxybenzamidine;
15 3-[(6-(pyridin-2-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-
hydroxybenzamidine;
3-[(6-(imidazolin-2-yl)-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-
10 hydroxybenzamidine; and
20 3-[(6-(piperidin-1-yl)methyl-2-[3-(1-methylimidazolin-2-yl)phenoxy]pyrimidin-4-yl)oxy]-4-
hydroxybenzamidine.

D. In a manner similar to that described above in Paragraph A, other compounds of the invention may be prepared.

- 15 15
25 EXAMPLE 2

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-
30 20 yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

A.	<u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	20.0%
35	Lactose	79.5%
	Magnesium stearate	0.5%

25 The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

B.	<u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	20.0%
40	Magnesium stearate	0.9%
30	Starch	8.6%
45	Lactose	69.6%
	PVP (polyvinylpyrrolidine)	0.9%

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then

50

5

- 34 -

dried, mixed with the magnesium stearate and formed into tablets with an appropriate tabletting machine.

10 C. Ingredients

10

5	Compound of the invention	0.1 g
	Propylene glycol	20.0 g
	Polyethylene glycol 400	20.0 g
	Polysorbate 80	1.0 g
15	Water	q.s. 100 mL

10 The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

20

D. Ingredients

% wt./wt.

15	Compound of the invention	20.0%
	Peanut Oil	78.0%
	Span 60	2.0%

25

The above ingredients are melted, mixed and filled into soft elastic capsules.

E. Ingredients

% wt./wt.

30

20	Compound of the invention	1.0%
	Methyl or carboxymethyl cellulose	2.0%
	0.9% saline	q.s. 100 mL

35

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

25

EXAMPLE 3

40

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

30

Ingredients

45

	Compound of the invention	0.02 g
	Propylene glycol	20.0 g
	Polyethylene glycol 400	20.0 g
	Polysorbate 80	1.0 g
50	0.9% Saline solution	q.s. 100 mL

5

10

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 m membrane filter and packaged under sterile conditions.

5

15

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

20

<u>Ingredients</u>	<u>% wt./wt.</u>
Compound of the invention	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

25

15 The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 5

30

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

35

<u>Ingredients</u>	<u>% wt./wt.</u>
Micronized compound of the invention	1.0%
Micronized lactose	99.0%

40

25 The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

EXAMPLE 6

45

30 This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

50

<u>Ingredients</u>	<u>% wt./wt.</u>
Compound of the invention	0.005%

5

Water	89.995%
Ethanol	10.000%

10

The compound of the invention is dissolved in ethanol and blended with water.

The formulation is then packaged in a nebulizer equipped with a dosing pump.

5

EXAMPLE 7

15

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 4-hydroxy-3-[(6-[3-(1-methylimidazolin-2-yl)phenoxy]-2-phenylpyrimidin-4-yl)oxy]benzamidine:

20

<u>Ingredients</u>	<u>% wt./wt.</u>
Compound of the invention	0.10%
Propellant 11/12	98.90%
Oleic acid	1.00%

25

15 The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

30

EXAMPLE 8

20 (*In vitro* assay for Factor Xa and Thrombin)

This assay demonstrates the activity of the compounds of the invention towards factor Xa, thrombin and tissue plasminogen activator. The activities were determined as an initial rate of cleavage of the peptide *p*-nitroanilide by the enzyme. The cleavage product, *p*-nitroaniline, absorbs at 405 nm with a molar extinction coefficient of 9920 M⁻¹cm⁻¹.

35 **Reagents and Solutions:**

40

Dimethyl sulfoxide (DMSO) (Baker analyzed grade).

Assay buffer:

30 50 mM TrisHCl, 150 mM NaCl, 2.5 mM CaCl₂, and
0.1% polyethylene glycol 6000, pH 7.5.

45

Enzymes (Enzyme Research Lab.):

1. Human factor Xa stock solution: 0.281 mg/mL in assay buffer, stored at -80°C (working solution (2X): 106 ng/mL or 2 nM in assay buffer, prepare prior to use).
2. Human thrombin stock solution: Concentration as specified by the supplier, stored at -80°C (working solution (2X): 1200 ng/mL or 32 nM in assay buffer,

50

5

prepare prior to use).

10

3. Human tissue plasminogen activator (tPA) (Two chains, Sigma or American Diagnostica Inc.) stock solution: Concentration as specified by the supplier, stored at -80°C (working solution (2X): 1361 ng/mL or 20 nM in assay buffer, prepare prior to use).

5

Chromogenic substrates (Pharmacia Hepar Inc.):

15

1. S2222 (FXa assay) stock solution: 6 mM in deionized H₂O, store at 4°C (working solution (4X): 656 μM in assay buffer).
2. S2302 (Thrombin assay) stock solution: 10 mM in deionized H₂O, stored at 4°C (working solution (4X): 1200 μM in assay buffer).
3. S2288 (tPA assay) stock solution: 10 mM in deionized H₂O, stored at 4°C (working solution (4X): 1484 μM in assay buffer for Sigma tPA, or 1120 μM for American Diagnostica tPA).

20

Standard inhibitor compound stock solution:

25

- 15 5 mM in DMSO, stored at -20°C.

Test compounds (compounds of the invention) stock solutions:

10 mM in DMSO, stored at -20°C.

Assay procedure:

30

Assays were performed in 96-well microtiter plates in a total volume of 200 μL.

20

- 20 Assay components were in final concentration of 50 mM TrisHCl, 150 mM NaCl, 2.5 mM CaCl₂, 0.1% polyethylene glycol 6000, pH 7.5, in the absence or presence of the standard inhibitor or the test compounds and enzyme and substrate at following concentrations: (1) 1 nM factor Xa (0.1 nM or 0.2 nM factor Xa for compounds with K_iXa in low picomolar range) and 164 μM S2222; (2) 16 nM thrombin and 300 μM S2302; (3) 10 nM tPA and 371 μM or 280 μM S2288. Concentrations of the standard inhibitor compound in the assay were from 5 μM to 0.021 μM in 1 to 3 dilution. Concentration of the test compounds in the assay typically were from 10 μM to 0.041 μM in 1 to 3 dilution. For potent test compounds, the concentrations used in the factor Xa assay were further diluted 100 fold (100 nM to 0.41 nM) or 1000 fold (10 nM to 0.041 nM). All substrate concentrations used are equal to their K_m values under the present assay conditions. Assays were performed at ambient temperature.

35

- 40 The first step in the assay was the preparation of 10 mM test compound stock solutions in DMSO (for potent test compounds, 10 mM stock solutions were further diluted to 0.1 or 0.01 μM for the factor Xa assay), followed by the preparation of test 45 compound working solutions (4X) by a serial dilutions of 10 mM stock solutions with

50

55

5

- 38 -

Biomek 1000 in 96 deep well plates as follows:

- (a) Prepare a 40 μ M working solution by diluting the 10 mM stock 1 to 250 in assay buffer in 2 steps: 1 to 100, and 1 to 2.5.
- (b) Make another five serial dilutions (1:3) of the 40 μ M solution (600 μ L for each concentration). A total of six diluted test compound solutions were used in the assay.

10

Standard inhibitor compound (5 mM stock) or DMSO (control) went through the same dilution steps as those described above for test compounds.

15

The next step in the assay was to dispense 50 μ L of the test compound working solutions (4X) (from 40 μ M to 0.164 μ M) in duplicate to microtiter plates with Biomek. To this was added 100 μ L of enzyme working solution (2X) with Biomek. The resulting solutions were incubated at ambient temperature for 10 minutes.

20

To the solutions was added 50 μ L of substrate working solution (4X) with Biomek.

25

15 The enzyme kinetics were measured at 405 nm at 10 seconds intervals for five minutes in a THERMOmax plate reader at ambient temperature. When a lower concentration of factor Xa was needed in the factor Xa assay, the enzyme kinetics were measured for fifteen minutes (0.2 nM factor Xa) or thirty minutes (0.1 nM factor Xa) at ambient temperature.

30

20 Calculation of K_i of the Test compounds:

35

Enzyme initial rates were calculated as mOD/min based on the first two minutes readings. The IC₅₀ values were determined by fitting the data to the log-logit equation (linear) or the Morrison equation (non-linear) with an EXCEL spread-sheet. K_i values were then obtained by dividing the IC₅₀ by 2. Routinely, K_i (factor Xa) values less than 3 nM were calculated from the Morrison equation.

40

Compounds of the invention, when tested in this assay, demonstrated the selective ability to inhibit human factor Xa and human thrombin.

EXAMPLE 9

45

30 (*In vitro* assay for Human Prothrombinase)

50

This assay demonstrates the ability of the compounds of the invention to inhibit prothrombinase. Prothrombinase (PTase) catalyzes the activation of prothrombin to yield fragment 1.2 plus thrombin with meizothrombin as the intermediate. This assay is an end point assay. Activity of the prothrombinase is measured by activity of thrombin (one of the reaction products) or by the amount of thrombin formed/time based on a

5

thrombin standard curve (nM vs mOD/min). For determination of IC₅₀ (PTase) of the compounds of the invention, PTase activity was expressed by thrombin activity (mOD/min).

10

Materials:

5 **Enzymes:**

1. Human factor Va (Haematologic Technologies Inc., Cat# HCVA-0110) working solution: 1.0 mg/mL in 50% glycerol, 2 mM CaCl₂, stored at -20°C.
2. Human factor Xa (Enzyme Res. Lab. cat# HFXa1011) working solution: 0.281 mg/mL in assay buffer (without BSA), stored at -80°C.
- 10 3. Human prothrombin (FII) (Enzyme Res. Lab., Cat# HP1002) working solution: Diluted FII to 4.85 mg/mL in assay buffer (without BSA), stored at -80°C.

20

Phospholipid (PCPS) vesicles:

PCPS vesicles (80%PC, 20%PS) were prepared by modification of the method reported by Barenholz *et al.*, *Biochemistry* (1977), Vol. 16, pp. 2806-2810.

15 **Phosphatidyl serine** (Avanti Polar Lipids, Inc., Cat#840032):

25 10 mg/mL in chloroform, purified from brain, stored -20°C under nitrogen or argon.

Phosphatidyl Choline (Avanti Polar Lipids, Inc., Cat# 850457):

30 50 mg/ml in chloroform, synthetic 16:0-18:1 Palmitoyl-Oleoyl, stored at -20°C under nitrogen or argon.

35 **Spectrozyme-TH** (American Diagnostica Inc., Cat# 238L, 50 µmoles, stored at ambient temperature) working solution: Dissolved 50 µmoles in 10 mL dH₂O.

BSA (Sigma Chem Co., Cat# A-7888, FractionV, RIA grade).

40 Assay buffer: 50 mM TrisHCl, pH 7.5, 150 mM NaCl, 2.5 mM CaCl₂, 0.1% PEG 6000 (BDH), 0.05% BSA (Sigma, Fr.V, RIA grade).

For one plate assay, prepare the following working solutions:

45 1. Prothrombinase complex:

(a) 100 µM PCPS (27.5 µL of PCPS stock (4.36 mM) diluted to final 1200 µL with assay buffer.

50 (b) 25 nM Human factor Va: 5.08 µL of Va stock(1 mg/mL) was diluted to final 1200 µL with assay buffer.

45 (c) 5 pM Human factor Xa: Dilute factor Xa stock (0.281 mg/mL) 1:1,220,000 with assay buffer. Prepare at least 1200 µL.

55 Combine equal volumes (1100 µL) of each component in the order of PCPS, Va and

35 Xa. Use immediately or store in ice (bring to ambient temperature before use).

5 - 40 -

10 2. 6 μ M Human prothrombin (FII): dilute 124 μ L of FII stock (4.85 mg/mL) to final 1400 μ L with assay buffer.

15 3. 20 mM EDTA/Assay buffer: 0.8 mL of 0.5 M EDTA (pH 8.5) plus 19.2 mL assay buffer.

20 5. 4. 0.2 mM Spectrozyme-TH/EDTA buffer: 0.44 mL of SPTH stock (5 mM) plus 10.56 mL of 20 mM EDTA/assay buffer.

25 5. Test compounds (compounds of the invention):

30 Prepare a working solution (5X) from 10 mM stock (DMSO) and make a series of 1:3 dilution. Compounds were assayed at 6 concentrations in duplicate.

35 **10 Assay conditions and procedure:**

40 Prothrombinase reaction was performed in final 50 μ L of mixture containing PTase (20 μ M PCPS, 5 nM hFVa, and 1 pM hFXa), 1.2 μ M human factor II and varied concentration of the test compounds (5 μ M to 0.021 μ M or lower concentration range). Reaction was started by addition of PTase and incubated for 6 minutes at ambient

45 15 temperature. Reaction was stopped by addition of EDTA(buffer to final 10 mM. Activity of thrombin (product) was then measured in the presence of 0.1 mM of Spectrozyme-TH as substrate at 405 nm for 5 minutes (10 seconds intervals) at ambient temperature in a THEROrmax microplate reader. Reactions were performed in 96-well microliter plates.

50 20 In the first step of the assay, 10 μ L of diluted test compound (5X) or buffer was added to the plates in duplicate. Then 10 μ L of prothrombin (hFII) (5X) was added to each well. Next 30 μ L PTase was added to each well, mix for about 30 seconds. The plates were then incubated at ambient temperature for 6 minutes.

55 25 In the next step, 50 μ L of 20 mM EDTA (in assay buffer) was added to each well to stop the reaction. The resulting solutions were then mixed for about 10 seconds. Then 100 μ L of 0.2 mM spectrozyme was added to each well. The thrombin reaction rate was then measured at 405 nm for 5 minutes at 10 seconds intervals in a Molecular Devices microplate reader.

60 30 **Calculations:**

65 Thrombin reaction rate was expressed as mOD/min. using OD readings from the five minute reaction. IC₅₀ values were calculated with the log-logit curve fit program.

70 The compounds of the invention demonstrated the ability to inhibit pro-thrombinase when tested in this assay.

50

35

5

- 41 -

EXAMPLE 10*(In vivo assay)*

10

The following assay demonstrates the ability of the compounds to act as anti-coagulants.

15

5 Male rats (250-330 g) were anesthetized with sodium pentobarbital (90 mg/kg, i.p.) and prepared for surgery. The left carotid artery was cannulated for the measurement of blood pressure as well as for taking blood samples to monitor clotting variables (prothrombin time (PT) and activated partial thromboplastin time (aPTT)). The tail vein was cannulated for the purpose of administering the test compounds (*i.e.*, the 10 compounds of the invention and standards) and the thromboplastin infusion. The abdomen was opened *via* a mid-line incision and the abdominal vena cava was isolated for 2-3 cm distal to the renal vein. All venous branches in this 2-3 cm segment of the 20 abdominal vena cava were ligated. Following all surgery, the animals were allowed to stabilize prior to beginning the experiment. Test compounds were administered as an 15 intravenous bolus (t=0). Three minutes later (t=3), a 5-minute infusion of thromboplastin was begun. Two minutes into the infusion (t=5), the abdominal vena cava was ligated at both the proximal and distal ends. The vessel was left in place for 60 minutes, after which it was excised from the animal, slit open, the clot (if any) 25 carefully removed, and weighed. Statistical analysis on the results was performed 30 using a Wilcoxon-matched-pairs signed rank test.

25

The compounds of the invention, when tested in this assay, demonstrated the ability to
35 inhibit the clotting of the blood.

25

* * * *

40

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the 30 true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or 45 steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

50

55

Claims

5

10

15

20

25

30

35

40

45

50

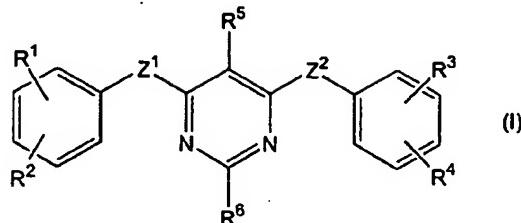
55

5

WHAT IS CLAIMED IS:

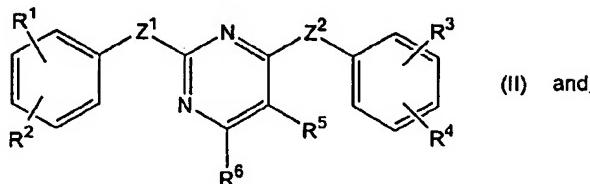
- 10 1. A compound selected from the group consisting of the following formulae:

10



15

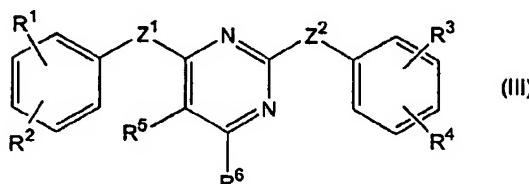
20



25

30

5



wherein:

35 Z¹ is -O-, -N(R⁷)-, -CH₂O- or -S(O)_n- (where n is 0 to 2);Z² is -O-, -N(R⁷)-, -OCH₂- or -S(O)_n- (where n is 0 to 2);R¹ and R⁴ are each independently hydrogen, halo, alkyl, nitro, -OR⁷, -C(O)OR⁷, 10 -C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -N(R⁷)C(O)R⁷, or -N(H)S(O)₂R⁸;

40

R² is -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(NH)N(H)C(O)OR⁹, -C(NH)N(H)C(O)R⁷, -C(NH)N(H)S(O)₂R⁹, or -C(NH)N(H)C(O)N(H)R⁷;

45

R³ is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, -OR⁷, -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -CH(OH)C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -R¹⁰-N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -N(R⁷)C(O)R⁷, 15 (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazoliny (optionally substituted by alkyl);

50

55

- 5 each R⁶ are independently hydrogen, halo, alkyl, haloalkyl, nitro, aralkoxy, -OR⁹, -R¹⁰-OR⁹, -N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -C(O)N(R⁷)CH₂C(O)N(R⁷)R⁸, -N(R⁷)C(O)N(R⁷)R⁸, -N(R⁷)C(O)R⁹, -N(R⁷)S(O)₂R⁸, or -N(R⁷)C(O)N(R⁷)-CH₂C(O)N(R⁷)R⁸;

10 5 each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, 10 monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocycl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein 15 the heterocycl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

20 15 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is 25 optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

30 25 each R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is 35 optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

40 30 each R¹⁰ is independently an alkylene or alkylidene chain; as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt 45 35 thereof.

- 5 2. The compound of Claim 1 wherein:
- Z¹ is -O-, -CH₂O- or -S(O)_n- (where n is 0 to 2);
- Z² is -O-, -OCH₂- or -S(O)_n- (where n is 0 to 2);
- R¹ and R⁴ are each independently hydrogen, halo, alkyl or -OR⁷;
- 10 5 R² is -C(NH)NH₂, -C(NH)N(H)S(O)₂R⁹, or -C(NH)N(H)C(O)N(H)R⁷;
- R³ is ureido, guanidino, -N(R⁷)R⁸, -N(R⁷)C(O)R⁷, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);
- 15 10 each R⁵ are independently hydrogen, halo, alkyl or haloalkyl;
- each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 20 15 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 25 20 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 30 25 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and
- 35 30 each R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino,
- 40 35 haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and
- 45 40 each R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino,
- 50 45 haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino,

5 monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl,
monoalkylaminocarbonyl, or dialkylaminocarbonyl).

10 3. The compound of Claim 2 wherein:

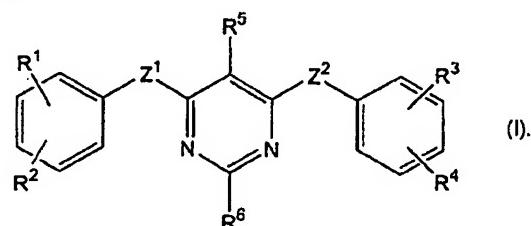
15 5 Z¹ is -O-;
Z² is -O-;
R¹ is hydrogen or -OR⁷;
R² is -C(NH)NH₂;
10 R³ is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl
(optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by
alkyl);
20 R⁴ is hydrogen;
each R⁵ is hydrogen or halo; and
each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy,
25 alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy,
alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or
dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo,
haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino,
monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl,
30 monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally
substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino,
dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl,
monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein
the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl,
35 hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy,
alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or
dialkylaminocarbonyl); and
40 each R⁷ is independently hydrogen or alkyl.

30 4. The compound of Claim 3 wherein:

45 Z¹ is -O-;
Z² is -O-;
R¹ is -OR⁷;
R² is -C(NH)NH₂;
50 R³ is (1,2)-imidazolyl (optionally substituted by methyl) or (1,2)-imidazolinyl (optionally
substituted by methyl);

- 5 R⁴ is hydrogen;
 R⁵ is hydrogen; and
 R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy,
 10 aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alcoxycarbonyl,
 aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and
 R⁷ is hydrogen or alkyl.

15 5. The compound of Claim 4 wherein the compound is selected from the
 formula (I):



20 20
 10
 25

25 30
 15

35 40

50

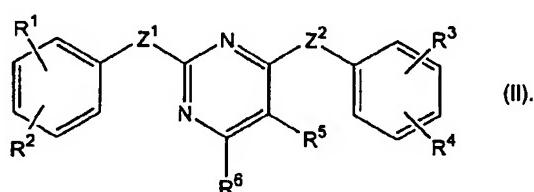
6. The compound of Claim 5 wherein:

- R¹ is hydroxy;
 R³ is 1-methylimidazolin-2-yl; and

15 R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy,
 aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alcoxycarbonyl,
 aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

35 7. The compound of Claim 6 wherein R⁶ is phenyl, i.e., namely the compound
 20 4-hydroxy-3-[[6-(3-(1-methylimidazolin-2-yl)phenoxy)-2-(phenyl)pyrimidin-4-
 yloxy]benzamidine.

40 8. The compound of Claim 4 wherein the compound is selected from the
 formula (II):



45 25

5

9. The compound of Claim 8 wherein:

R¹ is hydroxy;

R³ is 1-methylimidazolin-2-yl; and

10

5 R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

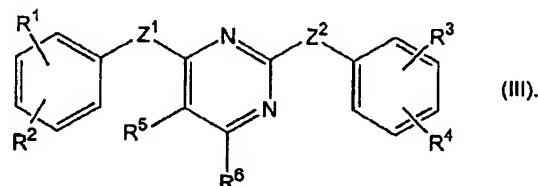
15

10 10. The compound of Claim 9 wherein R⁶ is phenyl, i.e., namely, the compound 4-hydroxy-3-[(4-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(phenyl)pyrimidin-2-yl]oxy]benzamidine.

20

11. The compound of Claim 4 wherein the compound is selected from the formula (III):

25



30

12. The compound of Claim 11 wherein:

R¹ is hydroxy;

R³ is 1-methylimidazolin-2-yl; and

35

20 R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

40

13. The compound of Claim 12 wherein R⁶ is phenyl, i.e., namely, the compound 4-hydroxy-3-[(2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(phenyl)pyrimidin-4-yl]oxy]benzamidine.

45

25 14. A pharmaceutical composition useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound selected from the group consisting of 30 the following formulae:

50

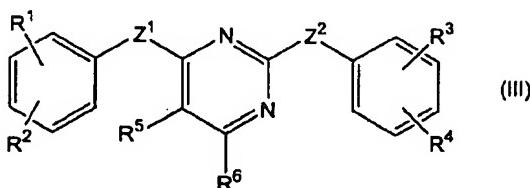
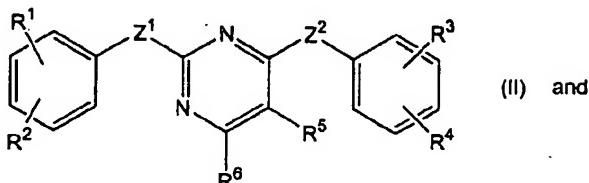
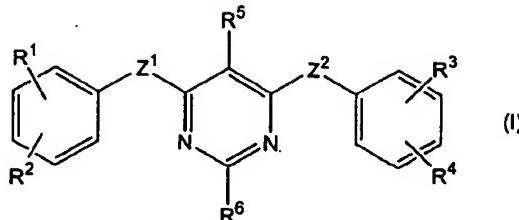
5

10

15

20

25



wherein:

Z¹ is -O-, -N(R⁷)-, -CH₂O- or -S(O)_n- (where n is 0 to 2);Z² is -O-, -N(R⁷)-, -OCH₂- or -S(O)_n- (where n is 0 to 2);5 R¹ and R⁴ are each independently hydrogen, halo, alkyl, nitro, -OR⁷, -C(O)OR⁷, -C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -N(R⁷)C(O)R⁷, or -N(H)S(O)₂R⁹;R² is -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(NH)N(H)C(O)OR⁹, -C(NH)N(H)C(O)R⁷, -C(NH)N(H)S(O)₂R⁹, or -C(NH)N(H)C(O)N(H)R⁷;R³ is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, -OR⁷, -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -CH(OH)C(O)N(R⁷)R⁸,-N(R⁷)R⁸, -R¹⁰-N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -N(R⁷)C(O)R⁷, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);45 15 each R⁵ are independently hydrogen, halo, alkyl, haloalkyl, nitro, aralkoxy, -OR⁹, -R¹⁰-OR⁹, -N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -C(O)N(R⁷)CH₂C(O)N(R⁷)R⁸, -N(R⁷)C(O)N(R⁷)R⁸, -N(R⁷)C(O)R⁸, -N(R⁷)S(O)₂R⁹, or -N(R⁷)C(O)N(R⁷)-CH₂C(O)N(R⁷)R⁸;

50

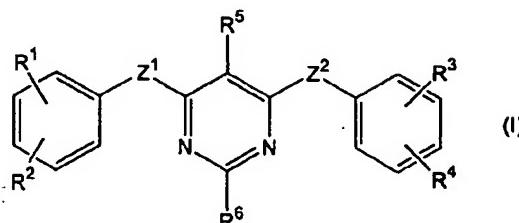
55

- 5 each R⁶ is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 10 5 each R⁷ and R⁸ is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 15 10 each R⁹ is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);
- 20 20 each R¹⁰ is independently an alkylene or alkylidene chain;
- 25 25 30 as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof,
- 30 40 and a pharmaceutically acceptable excipient.
- 35 45 15. A method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a

5

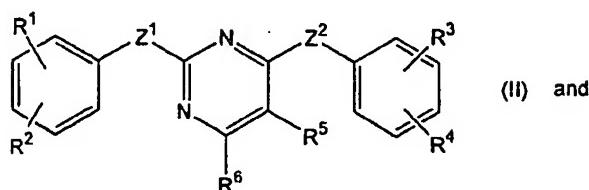
therapeutically effective amount of a compound selected from the group consisting of the following formulae:

10



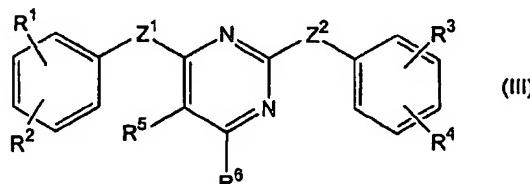
15

20



25

30



wherein:

5 Z¹ is -O-, -N(R⁷)-, -CH₂O- or -S(O)_n- (where n is 0 to 2);

Z² is -O-, -N(R⁷)-, -OCH₂- or -S(O)_n- (where n is 0 to 2);

35

R¹ and R⁴ are each independently hydrogen, halo, alkyl, nitro, -OR⁷, -C(O)OR⁷, -C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -N(R⁷)C(O)R⁷, or -N(H)S(O)₂R⁹;

R² is -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(NH)N(H)C(O)OR⁹, -C(NH)N(H)C(O)R⁷,

10 -C(NH)N(H)S(O)₂R⁹, or -C(NH)N(H)C(O)N(H)R⁷;

R³ is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, -OR⁷, -C(NH)NH₂, -C(NH)N(H)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸, -CH(OH)C(O)N(R⁷)R⁸, -N(R⁷)R⁸, -R¹⁰-N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -N(R⁷)C(O)R⁷.

45

15 (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolyl (optionally substituted by alkyl);

each R⁵ are independently hydrogen, halo, alkyl, haloalkyl, nitro, aralkoxy, -OR⁹, -R¹⁰-OR⁹, -N(R⁷)R⁸, -C(O)OR⁷, -R¹⁰-C(O)OR⁷, -C(O)N(R⁷)R⁸, -R¹⁰-C(O)N(R⁷)R⁸,

50

- | | | |
|----|--|--|
| 5 | $-C(O)N(R^7)CH_2C(O)N(R^7)R^8$, $-N(R^7)C(O)N(R^7)R^8$, $-N(R^7)C(O)R^8$, $-N(R^7)S(O)_2R^8$, or
$-N(R^7)C(O)N(R^7)-CH_2C(O)N(R^7)R^8$; | |
| 10 | each R^8 is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), heterocyclyl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or heterocyclylalkyl (wherein the heterocyclyl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); | |
| 15 | each R^7 and R^8 is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); | |
| 20 | each R^8 is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), and | |
| 25 | each R^{10} is independently an alkylene or alkylidene chain; as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof. | |
| 30 | each R^8 is aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); | |
| 35 | each R^7 and R^8 is independently hydrogen, alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (wherein the aryl is optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); | |
| 40 | each R^8 is alkyl, aryl (optionally substituted by halo, haloalkyl, alkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), and | |
| 45 | each R^{10} is independently an alkylene or alkylidene chain; as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof. | |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/28537

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/495; C07D 239/24
 US CL : 544/309, 310, 311, 319, 320; 514/274, 275.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. : 544/309, 310, 311, 319, 320; 514/274, 275.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/02470 A1 (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V.) 03 February 1994 (03/02/94), see entire document, especially page 1-3.	1-15
A	US 5,691,364 A (BUCKMAN ET AL) 25 November 1997 (25/11/97), see entire document, especially column 1-5.	1-15
A	DELIA, T.J. et al. Ring-Based Analogues of Pentamidine Versus P. Carinii Pneumonia in Culture. <i>Bioorganic & Medicinal Chemistry Letters</i> . 27 August 1996, Vol 6, No. 19, pages 2367-2370.	1-15

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
"A"	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"Z"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search		Date of mailing of the international search report	
14 February 2000 (14.02.2000)		07 MAR 2000	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Prithviraj Lawrence</i> Veerabaraman Balasubramanian Telephone No. (703) 308-1235	

Form PCT/ISA/210 (second sheet) (July 1998)

THIS PAGE BLANK (USPTO)